UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,709	10/18/2001	Albrecht Sippel	WEICKM-13	7039

23599 7590 08/12/2003

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	11

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,709	Applicant(s) SIPPEL ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,8,10-17,25,37,38,45,48-59 and 61-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9,18-24,26-36,39-44,46,47 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 3-4, 7, 8, 10-17, 25, 37, 38, 45, 48-59, 61-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

2. Applicant's election with traverse of Group I, and subgroups A2, B1, C1 (C-i), D2, and E1 in Paper Nos. 8 and 10 is acknowledged. The traversal is on the ground(s) that the restriction is improper in that no undue burden is created by searching all of the claimed inventions. In short, the applicant does not believe that searching the various claimed compositions, each having a different mode of operation, and comprising different compounds would be unduly burdensome. This is not found persuasive because, as indicated in the restriction requirement, each such mode of operation, and each different set of compounds, does require a different search. A separate search is required for each of the potential substituents of the various parts of the claimed recombinant cells and cell membranes.

The Applicant also argues in traversal that the subgroups A2-A5 are all kinases, and that there would therefore be no undue burden in searching each of them. This is also not found persuasive as the Examiner would be required, absent restriction, to search for the use, or the motivation to use, each of the individual kinases in a recombinant cell receptor. The fact that

they all share a common family, without more, is not evidence that there is no burden in the separate searches.

With regards to the receptors of subgroups C-i, C-ii, and C-iv, and the Applicant argues that the various subinventions are either "not separated from one another in the cell," and that therefore no searching burden is shown. This is not understood, or persuasive. The placement of various types of receptors on a cell is irrelevant to the search of the claimed invention. The Examiner is not examining cell structure, but is examining the teachings of individual receptors, and fragments thereof, in the art.

In response to the restriction of subgroups D-2 and D-3, the Applicant argues that "a number of inhibitors inhibit both kinases." However, in each embodiment of the claimed invention, it is not inhibitors of both kinases that are necessary, but inhibitors of either one individually. That some compounds may perform both functions does not demonstrate that a search for inhibitors of either kinase separately does not nullify the fact that inhibitors to the individual receptors is necessary. The fact that the same compound is used in different ways does not negate the necessity of demonstrating each of those separate functions individually.

Finally, the Applicant argues that "the Examiner has not established an undue searching burden in examining a scope broader than the subgroups set forth." The Examiner disagrees, and further disagrees with the Applicants' description of the restriction. The Examiner has not separated the broad from the narrow, but has separated numerous narrow inventions from each other. It is noted here, as it was in the restriction requirement, that any linking claims (i.e. broad claims) will be examined along with the elected narrow invention. If such linking claims are found allowable, then the subinventions falling within the linking claim will be rejoined.

However, absent such an allowable linking claim, there remains a need for non-coextensive, therefore burdensome, searches for each of the narrower claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use. The Applicant's attention is also directed to 37 CFR 1.77 (c), which states:

> (c) The text of the specification sections defined in paragraphs (b)(1) through (b)(11) of this section, if applicable, should be preceded by a section heading in uppercase and without underlining or bold type.

The guidelines suggested as the preferred layout are as follows:

TITLE OF THE INVENTION.
CROSS-REFERENCE TO RELATED APPLICATIONS.
STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
BRIEF SUMMARY OF THE INVENTION.
BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
DETAILED DESCRIPTION OF THE INVENTION.
CLAIM OR CLAIMS (commencing on a separate sheet).
ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate amendment of the specification is required.

4. The content of the present application's specification is objected to. In the application, the Applicant has included a number of Figures. However, there is no section of the specification providing the reference to, and brief description of, the drawing(s) as set forth in 37 CFR 1.74. Correction of the Specification is required.

Drawings

5. New corrected drawings are required in this application for the reason indicted in the attached Form PTO 948. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

6. Claim 5 is objected to because of the following informalities: it appears that the word "required" on line 2 of the claim should read as -- requires--. Appropriate correction is required.

7. Claim 18 is objected to because of the following informalities: The claim includes language describing the mediator section as able "to bind one or more adaptor proteins via which the effector protein or polypeptide which is capable of activating a Ras or Ras-like signal pathway in the cell... can bind the mediator section. In this description, there are two active

entities, the mediator section and the effector. It is suggested that the claim be amended to read such that the mediator section is able --to bind one or more adaptor proteins such that through the adaptor proteins, effector proteins or polypeptides are bound to the mediator section of the receptor.-- Such language would serve to clarify the focus of the claim.

Appropriate correction is required.

8. Claim 41 is objected to because of the following informalities: the article --a-- should precede the term "fusion protein" in line 2 of the claim. Appropriate correction is required.

9. Claim 43 is objected to because of the following informalities: in line 1 of the claims, the claim describes an assay for "determining the detecting the presence of..." It appears that the claim should read on methods of either --determining the presence of--, or on methods of --detecting the presence of-- ligands to the receptor. Appropriate correction is required.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1, 2, 5, 6, 9, 18-24, 26-29, and 60 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims all describe cells comprising membrane receptors with a ligand binding section, a membrane-localization signal, and a mediator section. While the applicant states that the receptors must be capable of binding to an effector protein, either directly or through an adaptor protein, the Applicant does not

indicate that such a capablility involves more than in required by naturally occurring cell receptors. Further, the Applicant does not require that the receptors be non-native (heterologous) to the cell. Thus, the claims read on naturally occurring cells comprising cell receptors that are native to the cell. Because such cells may be found in nature, these claims are rejected as reading on non-statutory subject matter.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 2, 5, 6, 9, 18-24, 26-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is treated as representative of the rejected claims. This claim describes a cell comprising a membrane receptor comprising a ligand binding section, a membrane localization signal, and a mediator section, that can bind to an effector section in a given status of ligand binding. However, the claim also describes effector and adaptor proteins without indicating whether such proteins are a necessary component of the claimed cell. I.e., the claim nowhere states that these proteins are a part of the claimed cell. It is therefore unclear whether or not the Applicant intends the parts of the claim relating to these proteins as necessary limitations of the claimed invention, or whether they are merely preset as a description as a possible function of the membrane receptor that is specifically included in the claimed cell.

Claim 1 also includes the language indicating that the effector protein binds to a component of a cell membrane "where appropriate via other proteins or polypeptides (adaptors), characterized in that the effector ...is in the form of a fusion protein of an effector section with an adaptor protein..." This language is unclear for two reasons. First, it is unclear whether the parenthetical reference to adaptors is a limitation on the other proteins of polypeptides, and identification of them, or an example of such other polypeptides or proteins. Second, the language first indicates that the presence of an adaptor protein or polypeptide is optional, then requires that the effector be in the form of a fusion protein comprising such an adaptor. The claim is therefore contradictory, and indefinite. It is not clear whether the adaptor protein is a required component to the described effector protein, or whether the effector protein must be in the form of the fusion of the adaptor and effector proteins.

14. Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims all describe embodiments of the claimed inventions wherein the effector protein is capable of activating a Ras or Ras-like signal pathway. However, the Applicant has not identified any characteristics, or provided any basis by which one of ordinary skill in the art could determine what is meant by the phrase "Ras-like signal pathway." It is noted that the specification states that the term "ras and ras-like signal pathway" includes "the so-called ras-like signal pathways which are controlled by various other members of the Ras family." However, the only example

of such family members is the human Ha-Ras, which appears to be a Ras protein. It is therefore not clear what meaning the Applicant intends to apply to the term "ras-like."

15. Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has been described above. Claim 2 further limits that claim to embodiments wherein the effector section is "a guanine nucleotide exchange factor (GEF) or an active protein from the Ras family." It is unclear what is meant by the term "an active protein." Further, it is unclear if, by the inclusion of this limitation, the Applicant intends that claim 1 and its depend claims may include embodiments wherein the effector protein is an inactive Ras protein.

16. Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 is treated as representative. This claim describes a mediator section that binds to one or more adaptor proteins through which an effector activates a Ras pathway, and wherein the adaptor makes possible the binding of the effector to a component of the cell membrane. It is unclear from the claim whether the effector is to be bound to the mediator section through the adaptor, or if the effector need not be bound to the mediator so long as the effector protein is able to bind to the membrane through an action of the mediator.

17. Claims 18-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In lines 4-7, the claim includes the language "in the form of a fusion protein of an effector section with an adaptor protein or polypeptide section which makes binding possible to the component of the membrane via one or more of the adaptor proteins." It is unclear how this clause relates to the rest of the claim.

Further, the clause describes a fusion protein that includes only a single adaptor protein, but also is capable of binding the "component of the membrane" through multiple adaptor proteins. It is unclear both as to how the fusion protein comprising a single adaptor protein makes possible binding to the membrane with multiple adaptors, and how this clause relates to the mediator section which is being defined by this claim.

18. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on the cell described in claim 1 above, wherein the "cell is a eukaryotic cell and, in particular, a yeast cell, specifically a yeast cell lacking cell walls." The claim language comprises a series of increasingly narrow classifications to describe the claimed cell.

Claim language providing for a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences

in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). Because the Applicant has in this case recited a set of increasingly narrow classifications of the claimed cell, it is unclear whether the phrases "in particular, a yeast cell," and "specifically a yeast cell lacking a cell wall" are intended as claim limitations, or as examples of eukaryotic cells that may be used in the claimed invention.

19. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim describes the claimed cell, wherein "it is applied to a solid carrier." It is unclear what is meant by the quoted language. More specifically, it is unclear whether the Applicant is indicating that the cell itself is immobilized to a solid carrier, or if the cell is being applied to a solid carrier to which a number of test ligands have been bound (i.e. as part of the assay for which cell is used), or if some other meaning is intended for the identified language.

20. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on methods for identifying receptor ligands comprising

contacting the claimed cells with a test substance "employed as fusion protein comprising a presumed ligand domain." It is not clear what a presumed ligand domain is. Because the claims are drawn, in part, to identifying peptide ligands, it is unclear if the term "presumed ligand domain" is intended to identify a subset of peptide ligands that may be incorporated into fusion proteins, or if the "presumed ligand domain" is another term intended to identify the peptide within the fusion protein.

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 1, 2, 5, 9, 18-24, 26, 27-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant cells wherein the Applicant has inserted a heterogeneous receptor into the cell, does not reasonably provide enablement for cells wherein the inserted receptors comprise portions of two or more receptors (e.g. the ligand binding domain of one receptor, and the transmembrane/cytoplasmic domain of another). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI

1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

In the specification, the applicant has indicated in the specification that the term membrane receptor includes receptors wherein the different domains of the receptor (ligand-binding, membrane-localization signal, and mediator) are derived from multiple receptors. See, App. pages 8-9. Thus, the claims read broadly on cells including either naturally occurring receptors, or synthetic receptors, such as those indicated in the statement of this rejection above. However, the Applicant has neither provided any working examples of such receptors, nor provided any guidance that would lead those in the art to such synthetic receptors.

It is noted that there is evidence in the art that some such receptors have been made, and that others may be possible. See e.g. Pacifica et al., WO 94/24958 (teaching the making and use of hybrid receptors such as those described by the Applicant). The reference discloses a single working example, refers to some previous working examples, and provides some general guidance to other receptors that may be combinable. Pages 4-7. However, the reference also states that "hybrid receptors comprising an extracellular domain from certain members of one receptor family and an intracellular domain from certain members of a heterologous receptor family posses biological activity..." Page 7, lines 19-25 (Note, the reference also indicates that the discovery that such receptors may be made was "unexpected"). The reference also states that,

while several hybrid receptors have been generated, only a few of them have been biologically active. Page 6, lines 7-10. Therefore, although this reference indicates that such receptors may be made, it also indicates that the art involved in making such receptors is unpredictable.

Presumably, part of the problem with this technology is the fact that those in the art are not currently able to predict or determine the way a protein of given sequence will fold. See e.g., Ngo et al., from The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds), Birkhauser, Boston 1994 (esp., pages 435-36, and 492, disclosing the difficulty of predicting the way a protein will fold from its sequence). However, while Ngo indicates that protein folding currently defies prediction, the function of proteins, including cell receptors, is highly dependant on the ability of these proteins to fold. See e.g., Bowie et al, Science 247:1306-10 (1990), page 1306, first paragraph. Bowie also indicates that the effect that mutations will have on a particular protein are likewise generally unpredictable. Id. Further, the more changes that are made to a sequence, the grater the effect on the protein function will be. See Wells, Biochemistry 29: 8509-17. It would be clear to those in the art that these teachings regarding the unpredictability of substitutions on protein function would apply equally to the creation of hybrid proteins (receptors) as indicated by the Applicant in the present application.

In view of the unpredictability involved in the making of hybrid receptors, the lack of guidance provided by the Applicant, and the limited guidance provided by the art, the Applicant in not enabled for the full scope of the claimed invention as it encompasses such synthetic (hybrid) protein receptors.

23. Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed cells and assays, wherein the claimed cells comprise tyrosine kinase, or tyrosine kinase associated, receptors, does not reasonably provide enablement for the elected invention wherein the receptor is a tyrosine kinase receptor, or to embodiments wherein the receptors' mediator section is associated with any tyrosine kinase, and the adaptor protein is a protein capable of binding an alpha unit of a G-protein (a Gα protein). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Applicant has described embodiments of the claimed inventions wherein the receptor is a tyrosine kinase, or tyrosine kinase associated receptors (e.g., App., p. 20), and embodiments wherein the adaptor protein is capable of binding to a Gα protein (App. p. 15). However, the Applicant has not provided any description in the specification, or any guidance, that would indicate to those in the art that adaptors that bind to Gα protein would be useful as adaptors to bind the effector to a tyrosine kinase, or tyrosine kinase associated, receptor mediator section. While the application does describe the two individual components, each of these components is described in the context of separate embodiments, with no apparent connection between them. Cf., App., pages 12-18 (describing embodiments wherein the receptor is a G-protein coupled receptor, and including embodiments where the adaptor is capable of binding to the Gα protein), with App., pages 18-22 (describing a separate embodiment wherein the receptors have intrinsic enzymatic activity, and embodiments wherein the adaptor is a Grb2 or Shc protein) and pages 22-24 (describing enzyme-coupled receptors, and indicating that similar adaptors may be used to

those of enzymatic receptors). Thus, the specification provides no guidance, or even any indication of how to make or use the elected embodiment of the claimed invention.

Further, while the art does indicate that specific Gα proteins can themselves bind to certain tyrosine kinases (See e.g. Bence et al., Nature 389: 296-99), and Jiang et al (Nature 395: 808-13), there is no evidence that these proteins are bind directly to any tyrosine kinase receptors. Thus, the art provides little guidance to those in the art as to the making and use of adaptors that can bind Gα proteins that would be effective adaptors for binding to the mediator section of either tyrosine kinase, or tyrosine kinase associated, receptors. This lack of teachings in the art is highlighted by the fact that G-protein coupled receptors and tyrosine kinase receptors are generally considered in the art to be separate cell signaling systems. See e.g., Trueheart et al., U.S. Patent 6,159,705, columns 23-27, and Lodish et al., Molecular Cell Biology, 3rd Ed, Scientific American Books, N.Y. (1995), pages 859, and 862-63 (describing tyrosine kinase receptors and G-protein coupled receptors as separate examples of receptors, and receptor signaling types in cells). See also, Jiang, page 811 (teaching that a Gα protein can inhibit the signal from a tyrosine kinase receptor (EGF), but also teaching that the mechanism through which it acts is by interfering with the downstream pathway, rather than direct binding to the receptor.) Thus, the art tends to teach away from the use of Gα binding proteins as adaptors to tyrosine kinase receptors.

Thus, the present application provides no guidance on the use of the Gα binding proteins as adaptors to bind to the mediator of tyrosine kinase receptors, and the art tends to indicate that the Gα protein does not bind to such receptors. In view of this, and in view of the large number of potential adaptors and receptors that may be used in the claimed invention, the broad scope of

the claims, and the limited teachings in the application and the art to guide those in the art in the practice of the elected invention, the claims are rejected for lack of enablement.

24. Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been described above. The claims describe a genus of inventions wherein any Gα binding protein may be used as an adaptor protein for use in targeting an activated Ras protein to the plasma membrane of a cell by binding to a tyrosine kinase receptor mediator section.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found

where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

However, as indicated above, the Applicant has not provided any examples of the claimed (elected) invention. There is no indication that the Applicant was in possession of any embodiment wherein an adaptor protein that is capable of binding to a Gα protein is used to target an effector to a tyrosine kinase receptor mediator section. Thus, the Applicant has not provided adequate written description to support claims covering the claimed and elected subject matter.

25. Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 46, 47, and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments of the claimed invention wherein the claimed cell comprises an active Ras protein, does not reasonably provide enablement for embodiments of the claimed invention wherein effector region of the effector protein comprises a Ras protein other than an active member of the Ras family. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims have been described above. As indicated above, claim 2 describes the claimed cell wherein the effector protein may be "an active protein from the Ras family." Because it is not clear what the purpose of the term "an active protein" is, or its effect on the claimed invention, the claim has the effect of implying that the cells of claim 1 may include effectors proteins wherein the effector sections may include non-active Ras family proteins. As

the Applicant has not described how the claimed methods would work where the effector protein is inactive, the Applicant is not enabled for such embodiments.

26. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim reads on embodiments wherein the fusion protein comprising the effector and adaptor proteins requires enzymatic modification before it can become bound to a membrane component. However, while the specification mentions that such a fusion may be made (page 11, lines 23-31), there are no working examples, or other guidance to lead those in the art to operative embodiments of such fusion proteins.

While the prior art teaches the use of fusion proteins to activate cell signal pathways (Jiang and Bence, supra), the proteins described in the art do not require any enzymatic action to themselves in order for them to bind to a surface component. It is also known in the prior art that, while fusion proteins may be made, the art of protein mutation and substitution is complex. See, discussion of effects of protein mutation with regards to the receptors above. By requiring that the fusion proteins of the present invention require further modification, the Applicant has added extra complexity to the claimed invention. Thus, the claims read on a broad class of inventions (any fusion protein requiring enzymatic modification) in a complex and unpredictable art, but the specification has not provided any guidance in the making or using of the claimed proteins. In

view of the above, the application is not found to have provided an enabling disclosure for the claimed invention.

27. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention has been described above. The claim reads on a class of cell comprising any fusion protein of any adaptor and effector, wherein the fusion protein requires enzymatic modification in order to become operative.

The written description requirements for a genus of invention have been described above. In the present case, the Applicant has identified the class of inventions by a functional limitation (the need for enzymatic modification). However, while the Applicant has claimed a broad genus of inventions, no working example of such fusion proteins have been provided. Nor is there any structural information by which those in the art may identify operable fusion proteins with the claimed function. Because the Applicant has not provided any written description by which those in the art could identify members of the claimed genus, the Applicant has not met the written description requirement for that genus of inventions.

28. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As indicated above, the claim reads on embodiments wherein the mediator protein of the claimed cell receptor is bound to several adaptor proteins.

There does not appear to any written description support for such an embodiment in the application. The application describes a specific instance wherein the adaptor portion of the effector fusion protein can bind to a second adaptor protein, which is in turn bound to the mediator. Page 21, lines 8-21However, in this case, the mediator itself is bound only to a single adaptor protein. This adaptor is then bound to another adaptor protein. The specification does not support embodiments where the mediator section itself binds to plural adaptors.

Claim Rejections - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. Claims 1, 2, 6, 9, 18-24, 26, 27, 30, 35, 36, 42, 43, 44, 47, and 60 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over

Trueheart et al., U.S. Patent 6,159,706. The claims read on the cells described above, and on methods of using these cells to identify ligands to the cell membrane receptors. The identified patent teaches the use of recombinant yeast cells modified to express heterologous cell surface receptors such that the cells may be used to identify ligands to the receptors. See e.g., claim 18. The patent teaches that, where a heterologous receptor is provided, the preferred embodiment also includes the inactivation of the homologous receptor (native to the cell). Col. 15, lines 13-15. Further, the reference teaches that the host cells for the heterogeneous receptor are cells wherein the receptor can activate a signal transduction pathway. Col. 15, lines 60-63. As an example of such a pathway, the patent discusses the yeast Ras pathway. Col. 16, lines 30-52. Because the reference teaches the inactivation of the native receptor, the reference inherently teaches embodiments wherein the signal pathway, hence a Ras pathway, cannot, "at least under certain conditions", be activated without the heterologous receptor.

While the patent does not indicate that the receptors are capable of interacting with the adaptor/effector fusion protein identified in the present claims, because the Applicant has not indicated that any special characteristics are required for such a capability, and because the claims as written do not require the presence of this fusion protein in the cell, the cells described in, and the methods claimed in the patent anticipate the identified claims.

31. Claims 1, 2, 6, 9, 18-21, 26, 27, 30, 35, 36, 39- 44, 47, 60, and claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart as applied to claims 1 and 30 (and others) above, and further in view of Ostanin et al. (U.S. Patent 6,251,605), and of Isakoff et al. (EMBO J 17(18): 5374-87), and Aronheim (Nuc Acids Res 25(16): 3373-74). Claim 31 further

limits the claimed cells to embodiments wherein the Ras pathways are made temperature sensitive. Claims 32 and 33 represent embodiments wherein the temperature sensitivity is caused by a mutation in the guanine nucleotide exchange factor (GEF) of the cell, with claim 33 further identifying a specific cell strain. This rejection is also drawn to the claimed cell comprising the effector/adaptor fusion protein.

As indicated above, Trueheart teaches that where the cells used in the assays have been made so as to express exogenous cell receptors, it is desirable to inactivate the homologous receptor native to the cell. Col 15, lines 13-15. However, the reference does not teach that this inactivation may be a conditional inactivation, such as by temperature sensitivity.

Ostanin also teaches yeast cells for use in identifying cell receptor ligands. See e.g., Col. 8, lines 42-50. The cells are also altered so as to express heterologous receptors. Id. Ostanin further teaches that, in order to facilitate assay interpretation, the endogenous "intrinsic" receptors are modified such that they are functionally distinct from the exogenous receptors. Col. 16, lines 59-65. Among the methods by which this may be done is by making the native receptor, or a protein necessary for its function (in the case of Ostanin receptor- the G protein with which the G-protein coupled receptor is associated), temperature sensitive. Thus, it would have been obvious to those in the art that the inactivation of the cell receptor pathways in the Trueheart cells need not be a complete inactivation, but that the cell signal pathways may also be conditionally inactivated such that the activities of the native receptors can be distinguished from those of the inserted receptors. Such conditional inactivation could, as per the teachings of Ostanin, include using temperature sensitive mutants of the host cell. However, neither Trueheart

nor Ostanin teaches that the cells may be made such that they have a temperature sensitive Ras pathway, wherein the pathway does not operate in the absence of the inserted receptor.

As indicated above, Trueheart teaches that the Ras signaling pathway of the yeast host cells can be substituted (complemented) by homologous Ras pathway components. The reference indicates that these complements can substitute for the loss of the native cell signal functions. Thus, it would have been obvious to those in the art that the inserted receptors could be made to induce signals in the cell through exogenously derived signal pathways.

Further, the Isakoff and Aronheim references each teach the use of Ras fusion proteins to activate the Ras pathway in a manner so as to rescue a host cell from temperature sensitivity (i.e. to bypass the temperature sensitive signal component). Aronheim teaches a method of using fusion proteins that allow signal pathway activation in the presence of an inactivating factor in a cdc25-2 yeast cell strain with a GEF mutation causing temperature sensitivity. See, page 3373, left column. Isakoff demonstrates the use of a similar system comprising a Ras fusion to an adaptor protein capable of binding to an activated cytoplasmic cell protein. Abstract, and page 5376. Thus, the reference teach the use of fusions of activated Ras to an adaptor protein that would lead to its placement at the cell's plasma membrane, and thereby activate the Ras signaling pathway.

The fusion proteins were used in these references to activate the pathways in temperature sensitive cells such that the pathways could be used to identify ligands activating cellular pathways. Id.; and Aronheim, abstract, and page 3373. It would therefore have been obvious to those in the art to have used such a system in the cells systems of Trueheart such that the fusion proteins would allow for the activation of a cellular pathway upon activation of the exogenous

receptor by a ligand thereto. This is because, from the teachings of Isakoff and Aronheim, it would have been obvious to those in the art that the activated Ras proteins could be fused to any ligand that would lead to the Ras effector being positioned at the plasma membrane such that it could activate a Ras pathway. As the reference teaches a method of allowing Ras pathway activation in the presence of a temperature sensitive inactivation, and as Ostanin teaches that such an inactivation is useful in facilitating assays such as those described in Trueheart, it would have been obvious combine these references to achieve the claimed ligand identification system.

Because the Ras fusion proteins were intended as signal pathway complements in pathway activation assays, and because Trueheart indicates that such complements may be used in the methods and cells disclosed in that patent, those in the art would have had a reasonable expectation of success in the combination of the references. This expectation would have been further strengthened by the success use of similar fusion in other protein-interaction assays. See e.g., Aronheim et al., Mol Cell Biol 17(6): 3094-3102. In view of the above, it would have been obvious to those in the art to have combined the identified references, thereby rendering the claimed cells and methods obvious.

In addition to the teachings above, Ostanin also identifies several substances that may be tested as ligands to the receptors. See, Col. 33, lines 19-22. The reference also teaches that a potential source of ligands is peptides derived from known ligands of the receptor. Col. 34, lines 47-67. Ostanin also teaches that the peptides may be placed in to fusion proteins. Col. 34, lines 13-33. It is assumed that the term "presumed ligand domains" includes the peptides derived from receptor ligands. As such, in view of the teachings of Ostanin, the reference renders obvious the limitations of each of claims 39-41.

32. Claims 1, 2, 6, 9, 18-21, 26, 27, 31-33, 35, 36, 42, 43, 44, 47, and 60 are rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, and Aronheim as applied against claim 31 above, and further in view of Pacifici et al., WO 94/29458 (Se also U.S. Patent 5,521,295). The claims have been described above. This rejection is concerned with embodiments wherein the receptor is a synthetic cell receptor (i.e. the receptor comprises portions of multiple receptors). Pacifici discloses the making and use of hybrid receptors, in particular a hybrid receptor derived from an erythropoietin receptor and an epidermal growth factor receptor. See, abstract, page 1, claims 1, 7, and 10. The reference further discloses that such receptors may be used for the identification of ligands for the receptor whose ligand-binding domain is present in the hybrid receptor. Page 6. The reference teaches that such receptors are useful because the hybrid receptor may be a means of linking a binding domain with unknown ligands to a intracellular domain with a known signal pathway, thereby facilitating the detection of ligand binding. Id. It would therefore have been obvious to use such hybrid receptors in the receptor ligand identification systems as described by the other references above.

There would have been a reasonable expectation of success, at least for certain embodiments due to the showing by Pacifici of activity in a disclosed hybrid receptor. See, pages 28-30. This reference, in combination with the others identified above, therefore renders obvious the claimed invention wherein the receptors are hybrid receptors.

33. Claim 34 is rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, and Aronheim as applied against claim 31 above, and further in view of

Mitsuzawa et al. (Genetics 123: 739-48), and DeClue et al. (Mol Cell Biol 11(6): 3132-38). Claim 34 further limits the cells of claim 31 to embodiments wherein the temperature sensitivity of the Ras pathway in induced by a mutation in the Ras protein of the host cell. The Trueheart, Ostanin, Isakoff, and Aronheim references have been described above. However, none of these references teach the making of a host cell with a temperature sensitive Ras pathway by mutating the Ras protein intrinsic to the cell. Such methods are taught, however, by each of the Mitsuzawa and DeClue references. Because the methods of circumventing the temperature sensitivity in host cells taught by Isakoff and Aronheim is not dependant on the presence of an active Ras protein, it would have been obvious to those in the art to achieve the temperature sensitive cell phenotype through the methods described by either Mitsuzawa or DeClue (depending on the type of host cell used).

34. Claims 1, 2, 6, 9, 18, 22-24, 26, 27, 30, 31-36, 39-44, 47, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart, Ostanin, Isakoff, Aronheim, Mitsuzawa, and DeClue as applied above, and further in view of either Jiang et al. (Nature 395: 808-13), or Bence et al. (Nature 289: 296-99) and in light of the teachings of Kawakami et al. (J Immunol 16: 1785-802), and Rawlings et al. (Science 271: 822-825). For the purposes of this rejection, it is assumed that the mediator itself need not be bound to the effector through the adaptor. This rejection is focused on the elected invention, wherein the receptor is, or is associated with, a tyrosine kinase (the mediator), the adaptor is a protein capable of binding to an alpha subunit of a G-protein, and the effector is a Ras protein. The references other than Jiang, Bence, Yang, and Kawakami have been described above. These other references teach the claimed cell comprising

an exogenous receptor for which ligand identification is desired, and the use of fusion protein of Ras to an adaptor protein which will target the Ras protein to the cell plasma membrane in a receptor dependant manner such that the binding of a ligand to the receptor will activate a Ras pathway. However, none of these references indicate that the adaptor protein may be a protein that binds to an alpha subunit (Gα) of a G protein where the mediator is a tyrosine kinase.

Jiang and Bence each teach that the Gα unit of a subset of G-proteins binds to, and is in part responsible for, the activation of the receptor mediated Bruton's tyrosine kinase (Btk). See, Jiang, page 809; and Bence, abstract. awakami teaches that Btk is activated downstream through a receptor associated tyrosine kinase. Page 1785, left column. See also, Yang et al., J Biol Chem 270: 20832-40, at 20839 (teaching that Btk is activated by activated cell receptors, and therefore as mediators of the receptor signals). Further, Rawlings et al. teaches that activated Btk is membrane associated. See, Abstract. Thus, from these references, it would be apparent that the Ras protein could be targeted to the cell surface membrane by attachment to a Gα protein binding protein. This is because the Gα protein is known to bind to proteins that have also been activated by cell surface receptors, and that, when activated, are membrane associated. From the teachings of Isakoff and Aronheim, those in the art would both be motivated to use the elected fusion protein such that the Gα would serve as a means of targeting the Ras protein to the cell membranes such that the Ras pathway could be activated, and the receptor ligand could be identified.

35. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, and Aronheim as applied against claim 1 above, and further in view of any of Ashby et al. (U.S. Patent 5,569,588) or Fink (U.S. Patent 5,532,157), and further in view of the Applicant's disclosure on pages 42, and 74. These claims read on embodiments wherein the claimed cells are "applied to a solid carrier" or "immobilized on biochips or enclosed in microchambers." For the purposes of this rejection, the claims are being read as though the Applicant intended to describe products wherein the cells themselves were attached to the surfaces, and the potential ligands then applied to the immobilized cells.

As described above, each of Trueheart and Ostanin teach the use of detectable gene products as indicators that ligands have bound to exogenous receptors on yeast cells. See, Trueheart, col. 14, lines 18-44, and Ostanin col. 8, lines 42-50, and col. 9, lines 48-67. However, these references do not teach the immobilization of the cells onto a surface. However, it would have been obvious to those in the art to have so immobilized the cells for these assays. This is because it is known in the art that assays may be conducted by, for example, applying the cells into microtiter plates. See e.g., Ashby, col. 6, lines 51-60; and Fink, col. 4, lines 46-48 (each reference teaching methods of detecting cell responses to substances wherein the cells are inserted into microtiter plates for the assays). Further, given that those in the art would have known that the cells could be immobilized, it would therefore have been obvious to use any such method or substrate for such immobilization. On pages 42 and 74 of the application, the Applicant has indicated that the use of biochips is known in the art. In these pages of the application, the Applicant specifically identifies the Wolf reference teaching the use of biochips

and indicates that methods of cell immobilization are known to those in the art. Thus, the limitations of claims 28 and 29 are obvious variations to the claimed invention.

Conclusion

36. No claims are allowed.

37. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Rine et al. (U.S. Patent 6,391,574). This patent teaches a yeast cell comprising a mutant version of the intrinsic Ras2 protein, wherein the mutant comprises a mutation making cells comprising the mutant sensitive to heat. See, Columns 28-29. The reference also teaches the use of cells comprising these mutations in assays for determining protein interactions. Col 3, lines 7-22. The reference is considered redundant to the Mitsuzawa reference.

Bai et al. (Oncogene 17: 941-48), and Lev et al. (WO 98/26054). These references teach various proteins, and protein motifs, that are used to connect tyrosine kinases to the Ras pathway. The references are relevant in that such proteins/motifs would be useful in the assays and methods as described by Trueheart, Ostanin, Isakoff, and Aronheim in that such proteins would be useful in making the fusion protein of the activated Ras such that they would bind to the tyrosine kinase receptor, and thereby localize the Ras to the cell membrane.

Wadsworth et al., J Biol Chem, 272(46): 28829-32. This reference teaches that an Gα protein is involved in the stimulation of a Ras pathway. The teachings of this reference are considered as related to those of the Jiang and Bence references above.

Klein et al., U.S. Application Publication 2003/0009022. This reference is considered relevant as its teachings are comparable to those of Trueheart and Ostanin above.

Wu et al., J Biol Chem, 273(13): 7197-7200 (March 1998). This reference teaches that the Gβγ G-protein subunit may be involved with the targeting of a protein from the cell cytosol to the cell membrane. Page 7197, right column. Thus, this reference, read in light of Isakoff and Aronheim, would suggest the use of this portion of the G-protein as an adaptor protein (thus an adaptor protein capable of binding the Gα protein). However, the

reference does not teach that this protein may be used to target the effector protein to a mediator section of a tyrosine kinase receptor.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
August 6, 2003

JAMES HOUSEL 8/8/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600